REMARKS/ ARGUMENTS

Applicant has carefully studied the non-final Examiner's Action mailed April 29, 2009, having a shortened statutory period for response set to expire, with one-month extension, on August 29, 2009. These explanatory remarks are believed to be fully responsive to the Action. Accordingly, this important patent application is now believed to be in condition for allowance.

Applicant responds to the outstanding Action by centered headings that correspond to the centered headings employed by Office, to ensure full response on the merits to each finding of Office.

Claim Rejections - 35 U.S.C. § 112

Applicant thanks Examiner Kim for holding the Examiner's Interview on July 30, 2009 with Applicant's representative, Robert Varkonyi. During the interview, the obviousness rejection was discussed; including that some references do not administer cells to ischemic cells, but healthy heart, and the art considers the administration of MSCs to ischemic heart to result in scar tissue.

Claim Rejections - 35 U.S.C. § 112

Claim 11 stands rejected under 35 U.S.C. § 112, paragraph 2, as indefinite. The Office found claim 11 provides an "umbilical cord blood composition[.]"[1] The Office noted that claim 11 depends upon claim 1, which provides an "umbilical cord blood cell composition" and points out claim 11 should reflect the same.[2] Applicant thanks the Office and has amended claim 11 accordingly. As such, it is respectfully requested that 35 U.S.C. § 112, paragraph 2 rejection of claim 11 be withdrawn.

Claim Rejections - 35 U.S.C. § 102

Claims 1, 6, 7, 9, 10, 12, 14 and 15 stand rejected under 35 U.S.C. § 102(b) as anticipated by *Isner, et al.* (U.S. Pat. No. 5,980,887). The Office found that "Isner et al. teach a method of treating cardiomyopathy or myocardial infarction ... by administering an effective amount of endothelial progenitor cells isolated from umbilical cord blood by intravenous infusion[.]"[3] The

[1] Page 2 of the non-final Office Action, dated April 29, 2009.
[2] Page 2 of the non-final Office Action, dated April 29, 2009.
[3] Page 3 of the non-final Office Action, dated April 29, 2009 (citing col. 3, lines 1-9; col. 6, lines 49-53; and col. 7, lines 16-22).

Office stated "[t]he endothelial progenitor cells isolated from umbilical cord blood is considered as an umbilical cord blood cell[.]"[4]

Applicant respectfully traverses the Office's finding, as *Isner, et al.* fails to disclose all elements of the claims, as required by MPEP 2131.[5] Applicant points out that *Isner, et al.* discloses using EC progenitors to enhance angiogenesis.[6] Claim 1 provides

> A method of treating a circulatory disorder selected from the group consisting of cardiomyopathy, myocardial infarction, and congenital heart disease, comprising: generating myocytes further comprising administering an effective amount of a composition comprising an umbilical cord blood cell to an individual with a circulatory disorder.

It is respectfully submitted that *Isner, et al.* does not disclose all the elements provided in claim 1. Therefore, *Isner, et al.* fails to anticipate claim 1, and those claims dependent thereon are patentable as a matter of law.[7] Accordingly, Applicant respectfully requests the Office withdraw the 35 U.S.C. § 102(b) rejection of claims 1, 6, 7, 9, 10, 12, 14 and 15.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 5-12 and 14-18 stand rejected under 35 USC 103(a) as obvious in light of *Pittenger, et al.* (U.S. Pat. No. 6,387,369), *Dengler, et al.* (Herz, 2002 Nov;27(7):598-610.), *Erices, et al.* (Br. J. Haematol. 2000, 109, 235-242), *Edelberg, et al.* (P.G. Pub. 2003/0091547) and *Lim, et al.* (Bone Marrow Transpl. 1999, 24, 965-970). The Office found that *Pittenger, et al.* discloses a method of regenerating cardiac muscle with mesenchymal stem cells (MSC), and introduction of MSC to a myocardial infarct reduced the degree of scar formation and augmented ventricular function.[8] The Office noted *Pittenger, et al.* fails to address the administration of umbilical cord blood cells (UCBCs), but found the invention obvious because *Dengler, et al.* "teach that UCBCs comprise stem cells with a capability of differentiating into cardiac myocytes ... Edelberg et al. teach that endothelial progenitor cells, which can also differentiate into cardiomyocytes, are also present in UCB ... and Isner et al. teach the use of endothelial progenitor cells derived from UCB in treating cardiovascular disorder[.]"[9] The Office concluded a skilled artisan would "recognize the suitability of UCBCs an alternative to MSCs of Pittenger

---

[4] Page 3 of the non-final Office Action, dated April 29, 2009.
[5] "To anticipate a claim, the reference must teach every element of the claim[.]"
[6] *Isner, et al.* (U.S. Pat. No. 5,980,887); abstract, column 2, lines 45-53; column 5, lines 21-25; column 6, lines 7-16.
[7] See, 35 U.S.C. § 112, paragraph 4.
[8] Page 4 of the non-final Office Action, dated April 29, 2009.
[9] Page 4 of the non-final Office Action, dated April 29, 2009.

et al. in the method of treating cardiovascular dysfunctions.[10] The finding of obviousness is traverses as (1) the combined references do not teach the claimed invention; and (2) the combination inappropriately alters the principle operation of a reference.

The references do not provide for the treatment of circulatory disorder by generating myocytes. Applicant points out there are differences between culturing stem cells with active cardiomyocytes and treating an infarcted area with dead cardiomyocytes and forming scar tissue. This was noted by *Dengler, et al.*, providing that transdifferentiation undertaken in many of the studies was due to cell fusion, and that further studies must consider the ischemically damages cardiac cells.[11] *Dengler, et al.*, states that more tests must be performed to "determine to what extent cellular engraftment exerts an active effect (i.e., contributes to contractile activity) vs a passive effect (i.e., prevention of infarct expansion and/or remodeling) on cardiac function."[12] Conversely, the present invention claims

> [a] method of treating a circulatory disorder selected from the group consisting of cardiomyopathy, myocardial infarction, and congenital heart disease, comprising: generating myocytes further comprising administering an effective amount of a composition comprising an umbilical cord blood cell to an individual with a circulatory disorder.

"In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious."[13] Considering the claimed invention as a whole, including inherent properties of the invention,[14] the composition must be administered to infracted regions to generate myocytes. It is submitted that these myocytes must be functional, i.e. be capable of contraction and electrical conduction, to treat the circulatory disorder. However, the present studies do not administer UCBC to infracted regions, and the art notes that current studies involving myocyte generation could result from fusion of the stem cells and live host cells.[15] The art also recognizes that studies must be undertaken to "assess

[10] Pages 4-5 of the non-final Office Action, dated April 29, 2009.
[11] See Dengler,. TJ, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 606, column 2.
[12] Dengler,. TJ, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 607, column 2 to page 608, column 1.
[13] MPEP 2141.02(I) (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 U.S.P.Q. 871 (Fed. Cir. 1983)) (emphasis in original).
[14] See, MPEP 2141.02(V).
[15] Dengler,. TJ, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 606, column 2.

responsiveness toward cardiomyogenic, endothelia, hepatic, neuronal, and pancreatic differentiation[,]"[16] indicating the art does not recognize the capacity for MSC to generate cardiomyocytes. "Since at least as early as Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 67, 43 S.Ct. 322, 67 L.Ed. 523 (1923), the concept of 'the invention as a whole' has comprised the total inventive act. That concept includes not only the remedy claimed but also the discovery of the source of persistent trouble despite the teachings of the prior art."[17] However, the prior art provides "it is not yet clear *if* and how injected or infiltrating stem cells ... electrically integrate into the surrounding myocardium."[18] *Dengler, et al.*, stresses the importance of replacement tissue integration, as "even small areas of imperfectly integrated tissues are likely to severely alter electrical conduction and syncytial contraction of the heart, with long-term life-threatening consequences."[19] It is respectfully submitted that all claim limitations "must be considered in judging the patentability of that claim against the prior art[,]"[20] and that the invention cannot be distilled to the gist of the invention.[21] The combined references fail to disclose the use in infarcted tissue, needed to generate functioning myocytes and treat circulatory disorder. Considering the claimed invention, as a whole, the combined references fail to disclose the invention, and therefore cannot obviate the claimed invention.

Additionally, the combined references do not teach the claimed invention. In the rejection, it was stated that it would be obvious to replace MSCs of *Pittenger, et al.* with UCBCs because *Dengler, et al.* provides stem cells in UCBCs possess the ability to differentiate into cardiac myocytes.[22] Applicant points out that the rejection does not provide a rationale why the stem cells of *Dengler, et al.* would be recognized as a suitable replacement for mesenchymal stem cells of *Pittenger, et al.* The mesenchymal stem cells of *Pittenger, et al.* are isolated from

---

[16] Kern, S. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006 May;24(5):1294-301. Epub 2006 Jan 12, page 1300, column 2.
[17] *In re Aufhauser*, 55 C.C.P.A. 1477, 1479, 399 F.2d 275, 277 (Cust. & Pat. App., Mol Biol Cell. 2005 Mar;16(3):1491-9. Epub 2005 Jan 12 1968) (citing *In re Antonson*, 272 F.2d 948, 47 CCPA 740, (1959); *In re Conover*, 304 F.2d 680. 49 CCPA 1205 (1962)).
[18] Dengler,. TJ, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 606, column 2 (emphasis added).
[19] Dengler,. TJ, et al. Stem cell therapy for the infarcted heart ("cellular cardiomyoplasty"), Herz. 2002 Nov;27(7):598-610, page 601 column 2.
[20] MPEP 2143.03 (citing *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970).
[21] MPEP 2141.02(II).
[22] Page 4 of the non-final Office Action, dated April 29, 2009.

adherent marrow or periosteal cells.[23] The Office does state that "it is well known in the art that UCBCs comprises [sic] mesenchymal progenitor cells according to Erices et al."[24] UCB contains stem and progenitor cells that are recognized in the art "to be quite distinct from those contained in bone marrow and adult peripheral blood."[25] Studies of bone marrow-derived MSC (BM-MSC) against UCB-derived MSC (UCB-MSC) found UCB-MSCs have unique marker staining from BM-MSCs,[26] and BM-MSCs have been shown to restore cardiac function with $CD34^+$ or $CD133^+$ cells, but no study have shown clear evidence of cardiomyogenesis.[27] Further, UCB-MSCs grow quicker than BM-MSCs, but generate fewer cells and senesce earlier than BM-MSCs,[28] and BM-MSCs have a wider differentiation range.[29] Therefore, Applicant respectfully submits that the mesenchymal stem cells derived from bone marrow are distinct from UCB-derived mesenchymal stem cells, and have different growing potential and differential potential.

The combination also fails to obviate the invention as the proposed modification changes the principle operation of a reference. Applicant notes that though *Inser, et al.* was not cited in the rejection, the reference was used in establishing the Office's *prima facie* case.[30] The *prima facie* case asserts that "Pittenger et al. teach a method of regenerating cardiac muscle ... and Inser et al. teach the use of endothelial progenitor cells derived from UCB in treating cardiovascular disorder[,]"[31] thus establishing that the combined references disclose treating cardiovascular disorders by regenerating cardiac muscle. It is respectfully pointed out that *Isner, et al.* does not regenerate muscle, but uses "EC progenitors ... to enhance angiogenesis ... to

[23] Pittenger, et al. (U.S. Pat. No. 6,387,369), column 2, lines 5-13 ("Homogeneous human mesenchymal stem cell compositions are obtained by culturing adherent marrow or periosteal cells[.]").
[24] Page 5 of the non-final Office Action, dated April 29, 2009.
[25] Nishiyama, N., et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 10, page 2017, column 2 to page 2018, column 1. See also, Terai, M. et al. Immortalization of human fetal cells: the life span of umbilical cord blood-derived cells can be prolonged without manipulating p16INK4a/RB braking pathway. Mol Biol Cell. 2005 Mar;16(3):1491-9. Epub 2005 Jan 12, page 1491, column 1.
[26] Kern, S. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006 May;24(5):1294-301. Epub 2006 Jan 12, page 1299, column 2.
[27] Nishiyama, N., et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 10, page 2022, column 1.
[28] Kern, S. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006 May;24(5):1294-301. Epub 2006 Jan 12, page 1297.
[29] Kern, S. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006 May;24(5):1294-301. Epub 2006 Jan 12, page 1299.
[30] See, page 4 of the non-final Office Action, dated April 29, 2009.
[31] Page 4 of the non-final Office Action, dated April 29, 2009.

sites of pathologic or utilitarian angiogenesis."[32] "The proposed modification cannot change the principle of operation of a reference[.]"[33] However, by changing the manner in which treatment is effected, from angiogenesis to muscle regeneration, the *prima facie* case of obviousness inappropriately alters the principle mode of operation of *Isner, et al.* Because the rejection alters the principle mode of operation of *Isner, et al.*, the reference cannot be used to establish a *prima facie* case of obviousness.

Accordingly, Applicant respectfully requests the Office withdraw the 35 USC 103(a) rejection of claims 1, 5-12 and 14-18.

Conclusion

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

Very respectfully,

SMITH & HOPEN

By: _____

Robert Varkonyi
Reg. No. 63,885
180 Pine Avenue North
Oldsmar, Florida 34677
Attorney for Applicant

Dated: August 31, 2009
Customer No. 21,901

CERTIFICATE OF FACSIMILE TRANSMISSION

(37 C.F.R. 1.8)

I HEREBY CERTIFY that this Amendment E, is being transmitted by facsimile to the United States Patent and Trademark Office, Art Unit 1651, Attn: Taeyoon Kim, (571) 273-8300 on August 31, 2009.

Dated: August 31, 2009

L Reeves

Lauren Reeves

[32] Isner, et al. (U.S. Pat. No. 5,980,887), Abstract; column 2, lines 50-56; column 3, lines 1-5.
[33] MPEP 2143.01(VI)